UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

08/256,418

SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/256,418	07/11/94	LASKY	L 833P1

EXAMINER	
GAMBEL, P	
ART UNIT	**PAPER NUMBER**
1816	4

18N1/1124

GINGER R. DREGER
GENENTECH, INC.
460 POINT SAN BRUNO BOULEVARD
SOUTH SAN FRANCISCO CA 94080-4990

DATE MAILED: 11/24/95

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

FOR RESTRICTION ONLY

☑ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 0 month(s), 30 days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133.

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☑ Claims 1-67 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☐ Claims _____ are rejected.
5. ☐ Claims _____ are objected to.
6. ☑ Claims 1-67 are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

DETAILED ACTION

1. Applicant's election of Group I (claims 1-14) and the species autoimmune disease (species A), rheumatoid arthritis (species H) and selectin (species A) in Paper No.6 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (M.P.E.P. § 818.03(a)). Upon reconsideration, claims 26-27, drawn to the CD34-specific pharmaceutical compositions used in the method claimed in Group I, have been regrouped with Group I. Claims 15-25, drawn to the nonelected invention of Group II, are withdrawn from consideration.

Claims 1-14 and 26-27 are under consideration and being acted upon.

2. Applicant should clarify the status and relationship of all parent applications on the first line of the specification.

3. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

4. Formal drawings and photographs have been submitted which fail to comply with 37 CFR 1.84. Please see the enclosed form PTO-948. Applicant is reminded to change the Brief Description of the Drawings (e.g. Figures 6A-B at the beginning of the description). Also applicant is requested to clarify whether Figure 2 is missing or simply has been omitted.

5. The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected. Appropriate corrections are required.

6. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-14 and 26-27 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention. In evaluating the facts of the instant case, the following is noted:

A) Applicant has not disclosed how to use CD34-specific pharmaceutical compositions either alone (claims 1-8, 12-13) or in combination with other reagents (e.g. selectins, integrins, anti-inflammatories, etc., claims 9-11) as a therapeutic regimen for human diseases. There is insufficient information or nexus with respect to using CD34-specific reagents to treat pathological conditions, commensurate in scope with the claimed invention, particularly with the predictability of treating the claimed and intended human diseases.

Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Since the therapeutic indices of immunosuppressive drugs biopharmaceutical drugs such as adhesion molecule inhibitors can be species- and model-dependent, it is not clear that reliance on the disclosed in vitro experimental results and the known in vivo animal studies accurately reflects the relative efficacy of the claimed therapeutic strategy and compositions.

The specification discloses that L-selectin was used to identify Sgp90(CD34) in mice and CD34 has been identified on endothelial cells both in mice and humans. In addition, applicant has disclosed the apparent L-selectin-Sgp90(CD34) interaction in mice only; it is not clear that human L-selectin-CD34 interactions occurs as well or how relevant this is to pathological conditions asscociated with leukocyte-endothelial adhesion. It is not clear how strong or how relevant such interactions are associated with leukocyte homing in vivo either in normal or disease conditions. There is insufficient information or nexus that either CD34 or L-selectin expression alone in murine and human tissues would be predictive for targeting the claimed CD34 specificities to inhibit pathological conditions associated with L-selectin-CD34 interactions, commensurate in scope with the claimed invention. The claimed invention is drawn to modulating human disease through L-selectin-CD34 interactions, however applicant has disclosed only limited information concerning such interactions in mouse experimental systems.

It is unclear from the specification whether the human L-selectin-CD34 interaction is key to human leukocyte-endothelial cell interaction. Applicant has exemplified some L-selectin-Sgp90(CD34) interaction in mice. Applicant and the prior art have exemplified CD34 on mouse and human endothelial cells. However, the criticality of L-selectin-CD34 interactions

in leukocyte-CD34 interactions, particularly in vivo under disease conditions, has not been demonstrated. Furthermore, it is not clear that the distribution and expression of CD34 in human tissues would provide sufficient targeting for the range of diseases targeted by the claimed methods. For example, is tissue expression of CD34 sufficient to block human leukocytes from adhering to endothelium associated with all of the acute and chronic inflammatory conditions claimed. There is insufficient information whether human leukocyte-mediated inflammation would operate through other known adhesion pathways to mediate inflammatory conditions that would obviate any inhibition through a CD34-mediated pathway. Therefore, the specification fails to enable the critical role or targeting CD34 in inhibiting human disease.

In addition, the CD34 specificity associated with the instant invention appears to rely on particular glycosylation modifications recognized by the MECA-79 antibody (see pages 31-32 of the specification, Discussion and Hemmerich et al., J. Exp. Med., 1994). Therefore, not all CD34 moieties or specificities appear to be appropriate for inhibiting leukocyte adhesion or function associated with the claimed invention to inhibit certain pathological conditions, encompassed by the claimed invention. Furthermore, there is insufficient information that the particular specificities recognized by the MECA-79 antibody on murine CD34 cells are the same on human CD34 cells and whether such specificities result in similar inhibition of human leukocyte-endothelial cell interactions.

In addressing adhesion-based therapy, Harlan states that whether you go humanized antibody, peptide, soluble receptor, or saccharide; it's still a long way to product (Edgington, Biotechnology, 1992; see entire document, particularly page 386, column 3, paragraph 4).

Ward et al. addresses the issues associated with selection of interventions of adhesion molecules as an approach to anti-inflammatory therapy (Therapeutic Immunol., 1994). At the current time of the article (1994), in humans there are relativley few conditions in which there is clear-cut evidence of the presence and participation of given adhesion molecules in humans (page 166, column 1, paragraph 1). Also, monoclonal antibodies are not likely to be the ultimate approach for in vivo blocking of adhesion molecules, even though they will likely provide important information (see pages 167-170, particularly Concluding Remarks). It is pointed out that, in spite of extensive development of peptide analogues for various inflammatory mediators and hormones, few if any of these products have found their way to routine clinical application (page 167, column 1, lines 1-23).

There appears to be insufficient evidence that applicant's reliance on the either L-selectin or CD34 expression alone would indicate that the claimed therapeutic modalities based upon CD34-specific antagonists would operate on either acute or chronic diseases, commensurate in scope with the claimed invention. Although an adhesion molecule-receptor pair may be expressed and play a role in leukocyte accumulation in various inflammatory conditions, the ability of an adhesion molecule antagonist to affect some therapeutic endpoint will depend on the adhesion molecule antagonist and the nature of the disease (e.g. acute versus chronic, tissue specificity, etc.). In humans, the claimed diseases encompassed by the claimed methods (see claims 7-8 for example) are already established before therapy is offered.

McMurray et al. (Sem. Arthritis Rhematism, 1994) discloses that the amelioration of a particular disease with a particular adhesion molecule antagonist was not predictive from one condition to another (see entire document, including Table 4). For example, L-selectin-specific antibodies have no effect on models of Sjogren's Syndrome, while decreasing incidence of diabetes in certain animal models (Table 4).

Albelda et al. (FASEB Journal, 1994) disclose that one of the most important lessons that has emerged from animal studies of CAMs is that there are distinct differences in the adhesion requirements for particular types of inflammation (pages 508-509, column 2, overlapping paragraph) and discloses the art known limitations of antibodies in treating human diseases (page 509, Therapeutic Approaches).

Different adhesion molecule specificities are appropriate for different acute and chronic inflammatory conditions. Applicant has not provided sufficient direction or guidance to indicate what are the appropriate combinations of CD34-specific antagonists and additional compounds set forth in claims 9-11 to treat the pathological conditions encompassed by the claimed invention. Therefore, in addition to the lack of predictability of treating the claimed pathological conditions with CD34-specific antagonists; there appears a lack of predictability of treating the claimed pathological conditions with CD34-specific antagonists in combination with selectin/integrin-specific inhibitors or anti-inflammatory reagents without more direction from the instant specification.

In view of the lack of predictability of the art to which the invention pertains the lack of established clinical protocols for effective adhesion-based (peptide/antibody-based) therapies, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for inhibiting cell/leukocyte-endothelial cell interactions.

B) It is unclear from the specification what is encompassed by claim 9's recitation of selectin, selectin ligand, an integrin, an integrin ligand, ligand other than CD34 polypeptide, a non-protein antagonist of L-selectin-CD34 interaction or antibodies to such molecules. Also, there is no evidence that such claimed compounds work as effective therapeutic agents in humans nor is there evidence that such compounds would work in combination with CD34-specific therapeutic agents. What are the metes and bounds of these claimed limitations? For example, what is encompassed by a non-protein antagonist of L-selectin-CD34 interaction. The disclosure is not enabled for the claimed methods using any selectin, integrin, etc., all of which are embraced by claim 9. Compositions comprising any of these compounds do not necessarily correlate with their ability to inhibit human pathology. The specification has not provided sufficient direction or guidance to one of skill in the art to properly select or administer any selectin, integrin, etc. that are required to practice the broadly claimed methods. It appears that undue experimentation would be required of one skilled in the art to practice the broadly claimed methods using the teaching of the specification alone.

C) The specification is objected to and claim 14 is rejected under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from a written description (e.g. sequenced); or (3) deposited.

It unclear if a cell line which produces an antibody having the exact structural and chemical identity of the MECA-79 antibody is known and publicly available, or can be reproducibly isolated without undue experimentation. Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed cell line; (2) a cell line which produces the chemically and functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event.

For example, very different V_H chains (about 50% homologous) can combine with the same V_K chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different V_H sequences combine with different V_K sequences to produce antibodies with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. [FUNDAMENTAL IMMUNOLOGY 242 (William E. Paul, M.D. ed., 3d ed. 1993)]. Therefore, it would require undue experimentation to reproduce the claimed antibody species MECA-79. Deposit of the hybridoma would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. See, 37 C.F.R. 1.801-1.809.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If the original deposit is made after the effective filing date of an application for patent, the applicant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state, that the biological material which is deposited is a biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which the case the statement need not be verified. See MPEP 1.804(b).

8. Claim 9(g)s is are rejected under 35 U.S.C. § 112, first and second paragraphs, as the claimed invention is not described in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the same, and/or for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 9(g) is indefinite in the recitation of "a non-protein antagonist of L-selectin-CD34 interaction" because the characteristics of the "antagonists" are not known. This language is vague and indefinite since it encompasses potentially thousands of different antagonists and it is not apparent from the disclosure which particular antagonists are being referred to. These "antagonists" could be any non-protein molecule that interferes with L-selectin-CD34 interactions in a direct or indirect manner, both known and unknown.

There is insufficient direction or guidance provided to assist one skilled in the art in the selection of such "antagonists" nor is there evidence provided that such "antagonists" would be effective in inhibiting L-selectin-CD34 interactions either in vitro or in vivo. It would require undue experimentation to produce all such possible antagonists without more explicit guidance from the disclosure. It would require undue experimentation to investigate all such antagonists. It appears that undue experimentation would be required of one skilled in the art to practice the claimed method using the teaching of the specification alone.

The applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter.

9. Claims 1-3, 9-14 and 26-27 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1-3, 9-14 are indefinite in the recitation of "inhibiting a pathological condition associated with intercellular adhesion mediated by L-selectin" and "a therapeutically effective amount" because it is not clear what is this association and whether a pathological condition is mediated by L-selectin adhesive events, and in turn,. what constitutes a therapeutically effective amount. Applicant should consider targeting inflammation or specific diseases, provided there is written support in the specification.

B) Claims 3-4 ares indefinite in the recitation of endothelial cells "on" peripheral or mesenteric lymph nodes because these cells are not on lymph nodes but are integral members of lymph nodes. Amendment should clearly define the appropriate relationship of endothelial cells and lymph nodes.

C) Claim 14 is indefinite in the recitation of "MECA-79" because its characteristics are not known. The use of "MECA-79" monoclonal antibody as the sole means of identifying the claimed antibody renders the claim indefinite because "MECA-79" is merely a laboratory designation which does not clearly define the claimed product, since different laboratories may use the same laboratory designation to define completely distinct cell lines or hybridomas.

D) Claim 13 is indefinite in the recitation of "a pharmaceutically active compound" because its characteristics are unclear.

E) Claims 26-27 are indefinite in the recitation of "composition". The specific function of the composition, the effective amount of the active ingredient and, minimally, the pharmaceutically acceptable carrier should be recited in the claims. Claims 24-25 as recited read on a compound per se.

F) Claim 27 is indefinite in the recitation of "an additional pharmaceutically active compound" because its characteristics are unclear. It is not clear what is encompassed by this claim language.

G) The amendments must be supported by the specification so as not to add any new matter.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

11. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a

whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

12. Claims 1-8, 12-14 and 26-27 are rejected under 35 U.S.C. § 102(e) as anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over Butcher et al. (U.S. Patent No. 5,538,724; see entire document). The instant claims are drawn to the use CD34-specific antagonists in therapeutic methods, and compositions comprising said CD34-specific antagonists.

Butcher et al. teaches the use of modulating leukocyte extravasation associated with inflammatory diseases encompassed by the claimed inventions (e.g. columns 3-6, Table 1) with the MECA-79 antibody (see entire document), soluble forms of the addressin identified by MECA-79 (e.g. column 5, paragraph 2) and various formulations and combinations of said antagonists (columns 3-6). Note that claim 27's recitation of pharmaceutically active compound is so open that it can encompass essentially any compound used in pharmaceuticals. The claimed and referenced methods and compositions appear to be the same. Although the reference is silent about the CD34 specificity, MECA-79 and the addressin identified by MECA-79 are the same as the claimed CD34 specificity.

It is the burden of the applicant to show the unobvious difference between the claimed and disclosed methods and compositions. See In re Best, 195 USPQ 430, 433 (CCPA 1977); In re Marosi, 218 USPQ 289, 292-293 (Fed. Cir. 1983); and Ex parte Novitski 26 USPQ 1389 (BPAI 1993)

13. Claims 1-8, 12-14 and 26-27 are rejected under 35 U.S.C. § 102(e) as anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over Lasky et al. (U.S. Patent No. 5,304,640) ; see entire document). The instant claims are drawn to the use CD34-specific antagonists in therapeutic methods, and compositions comprising said CD34-specific antagonists.

Lasky et al. (U.S. Patent No. 5,304,640) teaches the use L-selectin ligand Sgp90 antagonists including soluble Sgp90 and Sgp90-specific antibodies including the MECA-79 specificity (column 41) to treat inflammatory conditions encompassed by the claimed invention (see entire document, including section K. Therapeutic Compositions) . The claimed and referenced methods and compositions appear to be the same. Although the reference is silent about the CD34 specificity, Sgp90 and MECA-79 are the same as the claimed CD34 specificity.

It is the burden of the applicant to show the unobvious difference between the claimed and disclosed methods and compositions. See In re Best, 195 USPQ 430, 433 (CCPA 1977); In re Marosi, 218 USPQ 289, 292-293 (Fed. Cir. 1983); and Ex parte Novitski 26 USPQ 1389 (BPAI 1993)

14. Claims 1-14 and 26-27 are rejected under 35 U.S.C. § 103 as being unpatentable over Butcher et al. (U.S. Patent No. 5,538,724) or Lasky et al. (U.S. Patent No. 5,304,640) in view of Lasky et al. (CSHSQB, 1992; 1449, #35), Berg et al. (J. Cell Biol., 1991; 1449, 1449, #8) or Imai et al. (J. Cell Biol. 1991; 1449, #28), Sutherland et al. (Leukemia, 1988; 1449, #51), Lasky et al. (U.S. Patent No. 5,098,833; 1449, #2), Watson et al. (Nature, 1991; 1449, #55), Fina et al. (Blood, 1990; 1449, #22) and Schlingemann et al. (Lab. Invest., 1990; 1449, #42).

The instant claims are drawn to CD34-specific pharmaceutical compositions either alone or in combination with other reagents (e.g. selectins, integrins, anti-inflammatories), as a therapeutic regimen for human diseases.

Butcher et al. teaches the use of modulating leukocyte extravasation associated with inflammatory diseases encompassed by the claimed inventions (e.g. columns 3-6, Table 1) with the MECA-79 antibody (see entire document), soluble forms of the addressin identified by MECA-79 (e.g. column 5, paragraph 2) and various formulations and combinations of said antagonists (columns 3-6). Note that claim 27's recitation of pharmaceutically active compound is so open that it can encompass essentially any compound used in pharmaceuticals.

Lasky et al. (U.S. Patent No. 5,304,640) teaches the use L-selectin ligand Sgp90 antagonists including soluble Sgp90 and Sgp90-specific antibodies including the MECA-79 specificity (column 41) to treat inflammatory conditions encompassed by the claimed invention (see entire document, including section K. Therapeutic Compositions)

Butcher et al. and Lasky et al. differ from the instant claims by not explicitly stating that the MECA-79 and Sgp90 specificity is the same as the instant CD34 specificity as well as the use of other anti-inflammatory reagents in treating the targeted pathologies.

Berg et al. teach the MECA-79 antibody binds a 90 kD endothelial antigen which is a ligand for L-selectin and blocks lymphocyte attachment (see entire document, particularly the Discussion). This 90 kD endothelial antigen is the same Sgp90(CD34) molecule of the instant invention.

Imai et al. similarly teach the identification of the 90 kD endothelial ligand for L-selectin, which was inhibitable by the adhesion-blocking antibody MECA-79 (see entire document). Imai et al. also teach Sgp90-mediated binding was inhibitable by L-selectin-specific antibody and by specific polysaccharides (non-protein antagonists) (see page 1220, column 1, paragraph 3).

Lasky et al. (CSHSQB) teach the art-known role of L-selectin in leukocyte (see pages 259-260). Lasky et al. teach the 90 kD Sgp90 sulfated glycoprotein was a tissue-specific endothelial ligand for L-selectin whose role is to mediate lymphocyte trafficking to lymph nodes (see entire document, particularly page 263, column 1, lines 18-22 of text and pages 266-267). Lasky et al. further teaches that this 90 kD molecule acts as an endothelial adhesive ligand for lymphocyte trafficking and may act an inflammation-specific ligand (see page 266 column 1, paragraph 2). Here, Lasky et al. teaches that the art-known techniques of cloning and characterization of the cDNA encoding the 90 kD ligand would be the next step in defining its role in leukocyte-endothelial interactions (see page 266, bridging sentence of column 1-2). Such conventional characterization which would have included sequence comparisons by computer analysis would have determined that this 90 kD ligand was CD34. It is also noted that Lasky et al. cited CD34 as a similar adhesion molecule even before this analysis was done (see Conclusion).

In addition to Butcher et al. (U.S. Patent No. 5,538,724) or Lasky et al. (U.S. Patent No. 5,304,640); Berg et al., Imai et al. and Lasky et al. (5,098,833) all disclosed the 90 kD endothelial cell antigen as a ligand for L-selectin and the inhibition of such receptor-ligand interactions. These references differ from the instant invention in that they did not acknowledge the Sgp90 molecule was CD34, however such characterization was routine at the time the invention was made. This characterization would have included nucleic acid and amino acid sequence analysis that would have resulted in the determination that this 90 kD molecule was CD34 by art-known molecular and computer methods (for example, see the specification).

Sutherland et al. teach the structural characterization of the human CD34 antigen (see entire document), therefore the characterization of the murine Sgp90 as murine CD34 and, in turn, its homology to human CD34 would have been determined by standard sequence searching at the time the invention was made. These references differ from the instant claims by not teaching the presence of CD34 on human endothelial cells or the use of all of the pharmaceutical compositions alone or in combination in the claimed therapeutic methods.

Also, Lasky et al. (5,098,833) teach the art-known molecular, biochemical and immunologic techniques to derive therapeutic agents such as adhesion molecules, soluble adhesion molecule proteins, carbohydrate ligands (non-protein antagonists), adhesion molecule-specific antibodies and fusion proteins and their use as pharmacologic targeting agents (see entire document). Furthermore, Lasky et al. provides this teaching in the context of the claimed element L-selectin in the treatment of inflammatory conditions either alone (see column 20, paragraph 2) or in combination with other anti-inflammatory agents (see column 21, paragraph 3). The longterm known use of steroid and non-steroidal anti-inflammatories would have been encompassed by this reference.

In addition to above-mentioned inhibition of lymphocyte homing, Watson et al. also teach the use of soluble forms L-selectin to block neutrophil-mediated inflammation in vivo as well (see entire document).

Fina et al. teach the expression of CD34 in human tissues and implicate it as an adhesion molecule (see entire document).

Schlingemann et al. also teach the expression of CD34 in human tissues and, in particular, in association with endothelial microprocesses associated with adhesion and migration (see entire document).

Therefore, it was known at the time the invention was made that in vivo leukocyte-endothelial interactions could be inhibited through either member of the L-selectin/Sgp90 receptor/ligand pair. The skilled artisan would have highly motivated to further characterize Sgp90 by conventional techniques to determine that it was CD34, which was already characterized at the time the invention was made. This would have been further supported in the human system which had implicated CD34 expressed by endothelial cells in inflammatory sites and in leukocyte adhesion and migration. The use of either member of a receptor-ligand pair of an antibody specific for either (e.g. purified CD34 or antibodies to CD34) to inhibit such interactions was well known in numerous models of anti-adhesive therapy at the time the invention was made.

One of ordinary skill in the art at the time the invention was made would have been motivated to select and evaluate the efficacy of CD34-specific reagents to inhibit L-selectin-CD34 leukocyte-endothelial interactions as a therapeutic regimen in treating human inflammatory or autoimmune diseases. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

15. Claims 9-11 are rejected under 35 U.S.C. § 103 as being unpatentable over Butcher et al. (U.S. Patent No. 5,538,724) or Lasky et al. (U.S. Patent No. 5,304,640) in view of Lasky et al. (CSHSQB, 1992; 1449, #35), Berg et al. (J. Cell Biol., 1991; 1449, 1449, #8) or Imai et al. (J. Cell Biol. 1991; 1449, #28), Sutherland et al. (Leukemia, 1988; 1449, #51), Lasky et al. (U.S. Patent No. 5,098,833; 1449, #2), Watson et al. (Nature, 1991; 1449, #55), Fina et al. (Blood, 1990; 1449, #22) and Schlingemann et al. (Lab. Invest., 1990; 1449, #42) as applied to claims 1-14, and 26-27 above and in further view of Spertini et al. (J. Immunol., 1991; 1449, #45), Carlos et al. (Immunol. Rev., 1990; 1449, #17), Heavner et al. (U.S. Patent No. 5,464,935) and Butcher (Cell, 1991; 1449, #16).

Claims 9-11 are drawn to the use of a CD34-specific pharmaceutical composition in combination with other reagents (e.g. selectins, integrins) as a therapeutic regimen for human diseases.

In addition to teachings set forth above in section 14; Lasky et al. (U.S. Patent No. 5,098,833) above also taught the use of L-selectin anti-adhesive immunotherapy in combination with other anti-inflammatory agents. Therefore the art recognized the use and advantage of combination therapies in the treatment of inflammation.

Spertini et al. teach the increased effectiveness of inhibiting leukocyte-endothelial interaction by combining selectin- and integrin-specific antibodies including the use L-selectin as a member of the combination (see entire document, particularly Figures 2 and 4).

Carlos et al. teach the in vivo effectiveness of various selectin- and integrin-specific antibodies including the use of the L-selectin-specific MEL-14 antibody in anti-adhesion immunotherapy (see entire document, particularly Tables II and III).

Heavner et al. teaches the use of selectin inhibitors particularly P-selectin inhibitors for inflammatory diseases (see entire document). Heavner et al. also teach the role of multiple adhesion molecule-receptor mediated events in leukocyte adhesion, circulation and inflammation (see Background of the Invention).

Butcher et al. similarly teaches the role of multiple adhesion molecule-receptor mediated events in leukocyte adhesion and inflammatory processes.

One of ordinary skill in the art at the time the invention was made would have been motivated to select and evaluate the efficacy of CD34-specific reagents in combination with other anti-inflammatory agents to inhibit leukocyte-endothelial interactions as a therapeutic regimen in treating human inflammatory or autoimmune diseases. It is prima facie obvious to combine two compositions each of which is taught by prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

16. No claim is allowed.

17. Papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CMI Fax Center telephone number is (703) 308-4242 or (703) 305-7939.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1800 receptionist whose telephone number is (703) 308-0196.

Phillip Gambel, Ph.D.
Patent Examiner
Group 1800
September 30, 1996